Title	Tract-based spatial statistics (TBSS): application to detecting white matter tract variation in mild hypoxic-ischemic neonates
Author(s)	Gao, J; Li, X; Hou, X; Ding, A; Chan, KC; Sun, Q; Wu, EX; Yang, J
Citation	The 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS 2012), San Diego, CA., 28 August-1 September 2012. In IEEE Engineering in Medicine and Biology Society Conference Proceedings, 2012, p. 432-435
Issued Date	2012
URL	http://hdl.handle.net/10722/191626
Rights	IEEE Engineering in Medicine and Biology Society Conference Proceedings. Copyright © Institute of Electrical and Electronics Engineers.

34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

TRACT-BASED SPATIAL STATISTICS (TBSS): APPLICATION TO DETECTING WHITE MATTER TRACT VARIATION IN MILD HYPOXIC-ISCHEMIC NEONATES

Jie Gao [1], Xianjun Li [2], Xin Hou[1], Abby Ding[3], Kevin C. Chan[3,4], Qinli Sun[1], Ed X. Wu[3], and Jian Yang [1,2*]

1. Department of Radiology, the First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, China
2. Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, China
3. Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Hong Kong SAR, China
4. Departments of Ophthalmology and Bioengineering; Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA, USA

Abstract — **The aim of this study is to employ tract-based spatial statistics (TBSS) to analyze the voxel-wise differences in DTI parameters between normal and mild hypoxic-ischemic (HI) neonatal brains. Forty-one full term neonates (24 normal controls and 17 with mild HI injury) and 31 preterm neonates (20 normal controls and 11 with mild HI injury) underwent T1 weighted imaging, T2 weighted imaging and diffusion tensor imaging (DTI) within 28 days after birth. The voxel differences of fractional anisotropy (FA), λ1, λ2, and λ3 values between mild HI group and control group were analyzed in preterm and full term neonates respectively. The significantly decreased FA with increased λ2, λ3 in corticospinal tract, genu of corpus callosum (GCC), external capsule (EC) and splenium of the corpus callosum (SCC) in mild HI neonates suggested deficits or delays in both myelination and premyelination. Such impaired corticospinal tract, in both preterm and term neonates, may directly lead to the subsequent poor motor performance. Impaired EC and SCC, the additional injured sites observed in full term neonates with mild HI injury, may be causally responsible for the dysfunction in coordination and integration. In conclusion, TBSS provides an objective, independent and sensitive method for DTI data analysis of neonatal white matter alterations after mild HI injury.**

I. INTRODUCTION

Recent advances in neonatal care have markedly improved the survival rate and reduced the incidence of hypoxic-ischemic (HI) encephalopathy. Mild HI injury is becoming the major type in neonatal brain diseases, and is often correlated to behavioral anomalies and cognition impairments [1-3]. These injuries and subsequent delay in brain maturation are subtle and difficult to detect using conventional MRI. Diffusion tensor imaging (DTI) can highlight anatomical connectivity in the brain and other body organs [4-19]. Previous studies have demonstrated the ability and sensitivity of DTI to explore microstructural abnormalities due to HI injury in neonatal brain by measuring the anisotropic diffusion of water in white matter tracts [20-29].

Tract-based spatial statistics (TBSS) is a recently developed tool for DTI data analyzing, which allows objective voxel-wise analysis without limitations in image registration and smoothing [30]. It provides a powerful and objective method for detecting variation on major white matter tract. In this study, we aim to employ TBSS to test the voxel-wise differences in fractional anisotropy (FA), λ1, λ2 and λ3 between normal and mild HI neonatal brains in preterm and full term neonates.

II. METHOD

This study was approved by the local institutional review board. All parents of neonates were informed of the goals and risks of MR scanning with written consent before enrollment.

A. Subjects

All neonates who underwent conventional MRI within 28 days after birth were consecutively recruited and studied during 2010-2011. Those who were confirmed or suspected to have congenital malformations of central nervous system, congenital infections, metabolic disorders, hydrocephalus or brain injuries caused by any diseases except HI encephalopathy were excluded from this study.

Neonates in mild HI group fulfilled all of the following criteria: 1) evidences of fetal distress (fetal heart rate abnormalities or meconium-stained amniotic fluid) or neonatal distress (pH ≤ 7.2 in a umbilical cord blood and/or early neonatal arterial blood sample or APGAR score ≤ 7 at 1 min); 2) clinical signs of neonatal encephalopathy in the first 72 hours after delivery, i.e., abnormal consciousness (over-excitation, lethargy or coma), abnormal muscular tension (hypertonia or hypotonia), weak/absent primary reflexes or convulsions; and 3）abnormal MR appearances presented as local white matter injuries corresponding to mild HI changes [31]. Neonates in normal group fulfilled the following criteria: 1) no evidences of perinatal asphyxia history or other episodes that might cause cerebral damage; 2) without the above mentioned symptoms of neonatal encephalopathy; and 3) normal conventional MR appearances. Evaluation of the clinical history was performed by an experienced neonatal neurologist who was blind to the results of the brain conventional MRI examinations. The gestational

This work was supported by the grant from National Natural Science Foundation of China (No.81171317 & No.30970797 to Jian Yang) and the 2011 New Century Excellent Talent Support Plan from Ministry of Education of China to Jian Yang.

*Jian Yang is with the Department of Radiology, the First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, Shannxi, People's Republic of China. (The corresponding author to provide phone: 086-029-85323643; fax: 086-029-85225009; e-mail: yj1118@mail.xjtu.edu.cn).

age of each neonate was recorded and the postmenstrual age (PMA) at MR scan was calculated.

B. MR scan

The neonates were all sedated (oral chloral hydrate, 25-50 mg/kg) before MRI scanning. They were laid in a supine position and snugly swaddled in blankets to maintain temperature during the imaging procedure. Micro earplugs were prepared and placed in neonatal bilateral external acoustic meatus for the ear protection. The neonatal head was immobilized by molded foam, which was placed around the head during the imaging procedure. Heart rate and oxygen saturation were also monitored throughout the procedure. A pediatrician who experienced in resuscitation, was always present during each scan.

In this study, the three-dimensional magnetization prepared rapid gradient echo (3D-MPRAGE) T1 weighted images (T1WIs), fast spin echo (FSE) T2 weighted images (T2WIs) and DTI by single shot echo planar sequence were performed in a 3T scanner (GE, Signa HDxt) with 8-channel head coil. DTI was performed by 35 directions, b value=1000s/mm^2, SENSE factor = 2, TR/TE=5500/95ms, slice thickness = 4 mm without gap, field of view = 180mm×180mm, matrix = 256×256, voxel size = 0.70×0.70 ×4mm^3.

C. Data analysis

The analysis of DTI data was performed using the general linear model implemented in FMRIB's Software Library (FSL) [32]. Extracted brain images were acquired using Brain Extraction Tool (BET, package in the FSL) [33]. FMRIB's Diffusion Toolbox (FDT) [34] was used to carry out eddy current correction. FA, λ1, λ2 and λ3 of the diffusion tensor were calculated. TBSS was used to align FA images of all subjects to the target image (a representative FA image) and affine the aligned images into 1×1×1 mm^3 MNI152 standard space. Then the mean FA image and its skeleton were created. The aligned FA image of each subject was projected onto the mean FA skeleton (threshold = 0.2). Voxel-wise cross-subject statistics was performed to assess differences of FA, λ1, λ2, λ3 values between the mild HI group and control group using randomization with a general linear model that corresponds to two samples unpaired t-test. These analyses were performed in preterm and full term neonates respectively. All tests were taken to be significant at $p<0.05$.

III. RESULTS

41 full term neonates (17 neonates with mild HI injury, 24 neonates as normal control) with mean postmenstrual ages (PMA) of 39.51±1.77 weeks (range of 37-42 weeks) and 31 preterm neonates (11 neonates with mild HI injury, 20 neonates as normal control) with PMA mean of 35.31±0.95 weeks (range of 33-36 weeks) were enrolled in this study.

Mild HI injuries were presented as punctate white matter injury with hyperintensity in T1WIs and hypointensity in T2WIs and watershed white matter injury with hypointensity in T1WIs and hyperintensity in T2WIs. The demographic characteristics, including gestational age (GA), birth weight, ages at MR scan and PMA at MR scan, were all distributed without bias between mild HI group and normal group both in preterm and full term neonates (Tables I/II).

TABLE I. CLINICAL DATA IN NORMAL AND MILD HI GROUPS IN PRETERM NEONATES (MEAN VALUE ± SD)

Items	Normal Group (20 cases)	Mild HI Group (11 cases)	*P* value (independent sample t test)
Gestational age (weeks)	33.85±1.08	34.12±1.00	>0.05
Ages at MR scan （days）	10.85±5.28	7.18±3.55	>0.05
Birth weight (g)	1759.00±331.80	2151.82±617.93	>0.05
postmenstrual ages (PMA) at MR scan (weeks)	35.39±0.90	35.18±1.06	>0.05

TABLE II. CLINICAL DATA IN NORMAL AND MILD HI GROUPS IN FULL TERM NEONATES (MEAN VALUE ± SD)

Items	Normal Group (24 cases)	Mild HI Group (17 cases)	*P* value (independent sample t test)
Gestational age (weeks)	38.55±1.76	38.29±1.68	>0.05
Birth weight (g)	2711.67±746.04	2795.29±539.92	>0.05
Ages at MR scan （days）	7.71±3.03	8.18±5.02	>0.05
postmenstrual ages (PMA) at MR scan (weeks)	39.58±1.74	39.40±1.86	>0.05

The differences of FA, λ1, λ2 and λ3 values between mild HI and normal neonates were demonstrated by TBSS maps respectively in preterm group (Fig.1) and term group (Fig.2). The results of TBSS clearly showed the significantly decreased FA and increased λ2 and λ3 in multiple white matter tracts ($p<0.05$). These differences of DTI parameters between the mild HI and normal neonates were mainly located in cerebral peduncle (CP), posterior limb of internal capsule (PLIC) and corona radiata (CR) both in full term and preterm groups. Moreover, two additional regions with above changes of DTI parameters in full term neonates were found to be external capsule (EC) and splenium of the corpus callosum (SCC). In TBSS maps of λ1, the irregularly increased and decreased regions were found in certain discrete white matters.

IV. DISCUSSION

In this study, we demonstrated multiple white matter tract damages in neonates with mild HI injury by using TBSS analysis of DTI parameters. The impaired white matter structures were found to be more extensive than those observed in conventional MRI, which indicated the sensitivity and feasibility of TBSS DTI analysis.

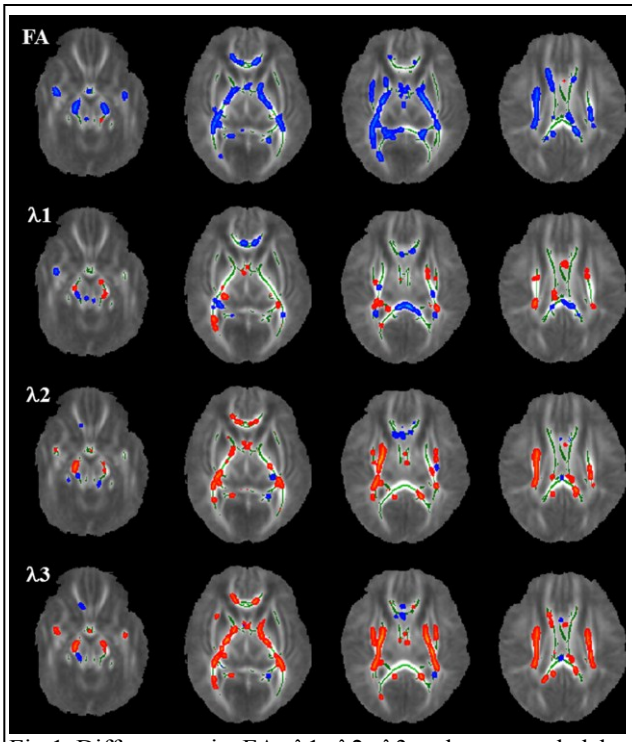

Fig.1 Differences in FA, λ1, λ2, λ3 values revealed by TBSS between mild HI and normal neonates in preterm group. Blue regions showed significantly decreased DTI parameters ($p<0.05$) in mild HI neonates relative to normal neonates. Red regions showed significantly increased DTI indexes ($p<0.05$) in mild HI neonates relative to normal neonates. Green regions represented the mean FA skeleton.

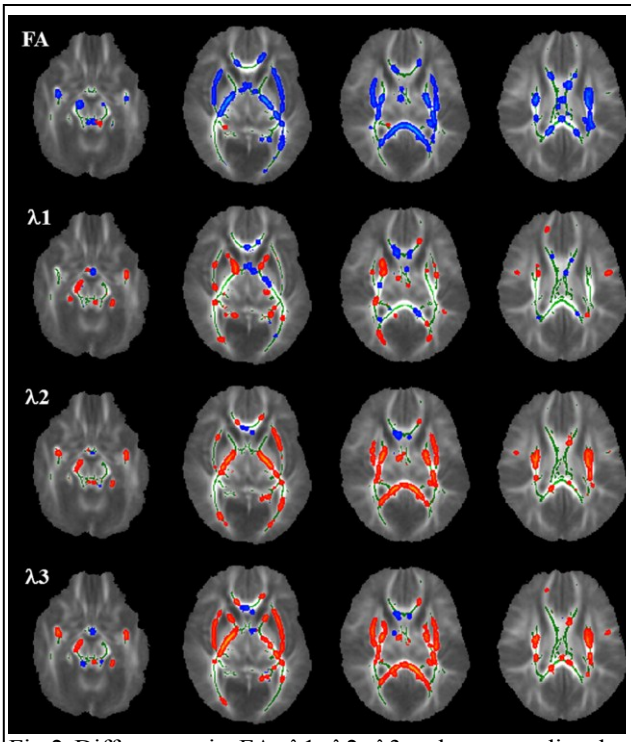

Fig.2 Differences in FA, λ1, λ2, λ3 values revealing by TBSS between mild HI and normal neonates in term group. Blue regions showed significantly decreased DTI parameters ($p<0.05$) in mild HI neonates relative to normal neonates. Red regions showed significantly increased DTI indexes ($p<0.05$) in mild HI neonates relative to normal neonates. Green regions represented the mean FA skeleton.

We found decreased FA in CP, PLIC and CR in all injured neonates. This suggested that these white matter tracts are primary sites to HI injury both in preterm and term neonates. We also analyzed three eigenvectors of the diffusion tensor. Our results showed that regions with FA decreases were accompanied by increased λ2 and λ3 (i.e., increased radial diffusivity). While the λ1, which contributes to axial diffusivity and reflects the number and diameter of axons, exhibit no obvious changes. These findings suggested that such mild HI white matter injury mainly led to deficits or delays in myelination, instead of damage on axons.

In full term neonates, EC and SCC, as the two additional injured sites in mild HI injury, exhibited increased radial diffusion. In fact, myelination of EC and SCC is after 42 weeks of PMA. This may indicate the HI damage to EC and SCC during the stage of premyelination in full term neonates. The premyelination process of EC and SCC in full term neonates is known to occur earlier than that in preterm neonates. Therefore these additional injured regions could be found in full term neonates.

A previous study has demonstrated that punctate lesions could lead to reduced myelination and cortical folding in preterm infants on conventional MRI [35]. Laura et al. also found reduced FA in PLIC in the infants with punctate lesions [20]. Our results were consistent with their findings under such mild brain injuries. However, our present findings indicated that impaired white matter tracts were more extensive, which was along the corticospinal tract (from CP to CR, including PLIC) in both preterm and term neonates with mild HI injury. These regions are closely interrelated with motor function, which suggest subsequent motor impairment with these neonates. The additional damage in EC and SCC of full term neonates, which belong to association fibers, may be related to subsequent dysfunction in coordination and integration.

In current study, TBSS, an observer independent and voxel-wise approach, was used to analyze DTI data. Although TBSS offers a number of advantages over the conventional evaluation methods, TBSS analysis is limited to the major WM tracts. Therefore, the voxel-based style analyses (VBA) will be performed in the future to observe the alterations in whole brain.

V. Conclusion

This is the first study to explore white matter injury in both preterm and term neonatal brains with mild HI injury by using TBSS for DTI data analysis. TBSS, as an objective and sensitive method, can reveal multiple white matter microstructural abnormalities in mild HI neonatal brains.

ACKNOWLEDGMENTS

The authors would like to thank Drs. He Wang, Zhikui Xiao, Zhenyu Zhou and Guang Cao from Applied Science Lab, GE Healthcare for their technical assistance.

REFERENCES

[1] A. Hall, *et al.*, "School attainment, cognitive ability and motor function in a total Scottish very-low-birthweight population at eight years: A controlled study," *Developmental Medicine and Child Neurology,* vol. 37, pp. 1037-1050, Dec 1995.

[2] F. F. Gonzalez and S. P. Miller, "Does perinatal asphyxia impair cognitive function without cerebral palsy?," *Archives of Disease in Childhood-Fetal and Neonatal Edition,* vol. 91, pp. F454-F459, Nov 2006.

[3] K. J. Steinman, *et al.*, "Neonatal Watershed Brain Injury on Magnetic Resonance Imaging Correlates With Verbal IQ at 4 Years," *Pediatrics,* vol. 123, pp. 1025-1030, Mar 2009.

[4] P. Mukherjee, *et al.*, "Normal brain maturation during childhood: Developmental trends characterized with diffusion-tensor imaging," *Radiology,* vol. 221, pp. 349-358, Nov 2001.

[5] V. J. Schmithorst, *et al.*, "Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: A cross-sectional diffusion-tensor MR imaging study," *Radiology,* vol. 222, pp. 212-218, Jan 2002.

[6] J. S. Shimony, *et al.*, "Quantitative diffusion-tenser anisotropy brain MR imaging: Normative human data and anatomic analysis," *Radiology,* vol. 212, pp. 770-784, Sep 1999.

[7] T. Klingberg, *et al.*, "Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study," *Neuroreport,* vol. 10, pp. 2817-2821, Sep 1999.

[8] J. J. Neil, *et al.*, "Normal brain in human newborns: Apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging," *Radiology,* vol. 209, pp. 57-66, Oct 1998.

[9] Y. Wu and E. X. Wu, "MR study of postnatal development of myocardial structure and left ventricular function," *J Magn Reson Imaging,* vol. 30, pp. 47-53, Jul 2009.

[10] X. G. Zhao, *et al.*, "Identifying rodent olfactory bulb structures with micro-DTI," *Conf Proc IEEE Eng Med Biol Soc,* vol. 2008, pp. 2028-31, 2008.

[11] Y. Wu, *et al.*, "MR study of the effect of infarct size and location on left ventricular functional and microstructural alterations in porcine models," *J Magn Reson Imaging,* vol. 29, pp. 305-12, Feb 2009.

[12] E. X. Wu, *et al.*, "MR diffusion tensor imaging study of postinfarct myocardium structural remodeling in a porcine model," *Magn Reson Med,* vol. 58, pp. 687-95, Oct 2007.

[13] K. C. Chan, *et al.*, "MRI of late microstructural and metabolic alterations in radiation-induced brain injuries," *J Magn Reson Imaging,* vol. 29, pp. 1013-20, May 2009.

[14] J. S. Cheung, *et al.*, "Diffusion tensor imaging of liver fibrosis in an experimental model," *J Magn Reson Imaging,* vol. 32, pp. 1141-8, Nov 2010.

[15] J. S. Cheung, *et al.*, "In vivo DTI assessment of hepatic ischemia reperfusion injury in an experimental rat model," *J Magn Reson Imaging,* vol. 30, pp. 890-5, Oct 2009.

[16] E. S. Hui, *et al.*, "B-value dependence of DTI quantitation and sensitivity in detecting neural tissue changes," *Neuroimage,* vol. 49, pp. 2366-74, Feb 1 2010.

[17] Q. Li, *et al.*, "Voxel-based analysis of postnatal white matter microstructure in mice exposed to immune challenge in early or late pregnancy," *Neuroimage,* vol. 52, pp. 1-8, Aug 1 2010.

[18] K. C. Chan, *et al.*, "In vivo multiparametric magnetic resonance imaging and spectroscopy of rodent visual system," *J Integr Neurosci,* vol. 9, pp. 477-508, Dec 2010.

[19] K. C. Chan, *et al.*, "In vivo evaluation of retinal and callosal projections in early postnatal development and plasticity using manganese-enhanced MRI and diffusion tensor imaging," *Neuroimage,* vol. 59, pp. 2274-83, Feb 1 2012.

[20] L. Bassi, *et al.*, "Diffusion Tensor Imaging in Preterm Infants With Punctate White Matter Lesions," *Pediatric Research,* vol. 69, pp. 561-566, Jun 2011.

[21] G. K. Malik, *et al.*, "Serial quantitative diffusion tensor MRI of the term neonates with hypoxic-ischemic encephalopathy (HIE)," *Neuropediatrics,* vol. 37, pp. 337-343, Dec 2006.

[22] O. Brissaud, *et al.*, "Efficiency of fractional anisotropy and apparent diffusion coefficient on diffusion tensor imaging in prognosis of neonates with hypoxic-ischemic encephalopathy: a methodologic prospective pilot study," *AJNR Am J Neuroradiol,* vol. 31, pp. 282-7, Feb 2010.

[23] J. Yang, *et al.*, "Manganese-enhanced MRI detection of neurodegeneration in neonatal hypoxic-ischemic cerebral injury," *Magn Reson Med,* vol. 59, pp. 1329-39, Jun 2008.

[24] J. Yang and E. X. Wu, "Detection of cortical gray matter lesion in the late phase of mild hypoxic-ischemic injury by manganese-enhanced MRI," *Neuroimage,* vol. 39, pp. 669-79, Jan 15 2008.

[25] K. C. Chan, *et al.*, "Late measures of microstructural alterations in severe neonatal hypoxic-ischemic encephalopathy by MR diffusion tensor imaging," *Int J Dev Neurosci,* vol. 27, pp. 607-15, Oct 2009.

[26] K. C. Chan, *et al.*, "Functional MRI of postnatal visual development in normal and hypoxic-ischemic-injured superior colliculi," *Neuroimage,* vol. 49, pp. 2013-20, Feb 1 2010.

[27] S. Wang, *et al.*, "Mild hypoxic-ischemic injury in the neonatal rat brain: longitudinal evaluation of white matter using diffusion tensor MR imaging," *AJNR Am J Neuroradiol,* vol. 30, pp. 1907-13, Nov 2009.

[28] S. Wang, *et al.*, "Characterization of white matter injury in a hypoxic-ischemic neonatal rat model by diffusion tensor MRI," *Stroke,* vol. 39, pp. 2348-53, Aug 2008.

[29] Y. Wang, *et al.*, "Comparing diffusion-weighted and T2-weighted MR imaging for the quantification of infarct size in a neonatal rat hypoxic-ischemic model at 24h post-injury," *Int J Dev Neurosci,* vol. 25, pp. 1-5, Feb 2007.

[30] S. M. Smith, *et al.*, "Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data," *Neuroimage,* vol. 31, pp. 1487-1505, Jul 2006.

[31] L. Liauw, *et al.*, "Hypoxic-ischemic encephalopathy: Diagnostic value of conventional MR imaging pulse sequences in term-born neonates," *Radiology,* vol. 247, pp. 204-212, Apr 2008.

[32] S. M. Smith, *et al.*, "Advances in functional and structural MR image analysis and implementation as FSL," *Neuroimage,* vol. 23, pp. S208-S219, 2004.

[33] S. M. Smith, "Fast robust automated brain extraction," *Human Brain Mapping,* vol. 17, pp. 143-155, Nov 2002.

[34] T. E. J. Behrens, *et al.*, "Characterization and propagation of uncertainty in diffusion-weighted MR imaging," *Magnetic Resonance in Medicine,* vol. 50, pp. 1077-1088, Nov 2003.

[35] L. A. Ramenghi, *et al.*, "Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions," *Neuroradiology,* vol. 49, pp. 161-7, Feb 2007.